# Informed Consent and Returning Results in Whole-Exome Sequencing Protocols

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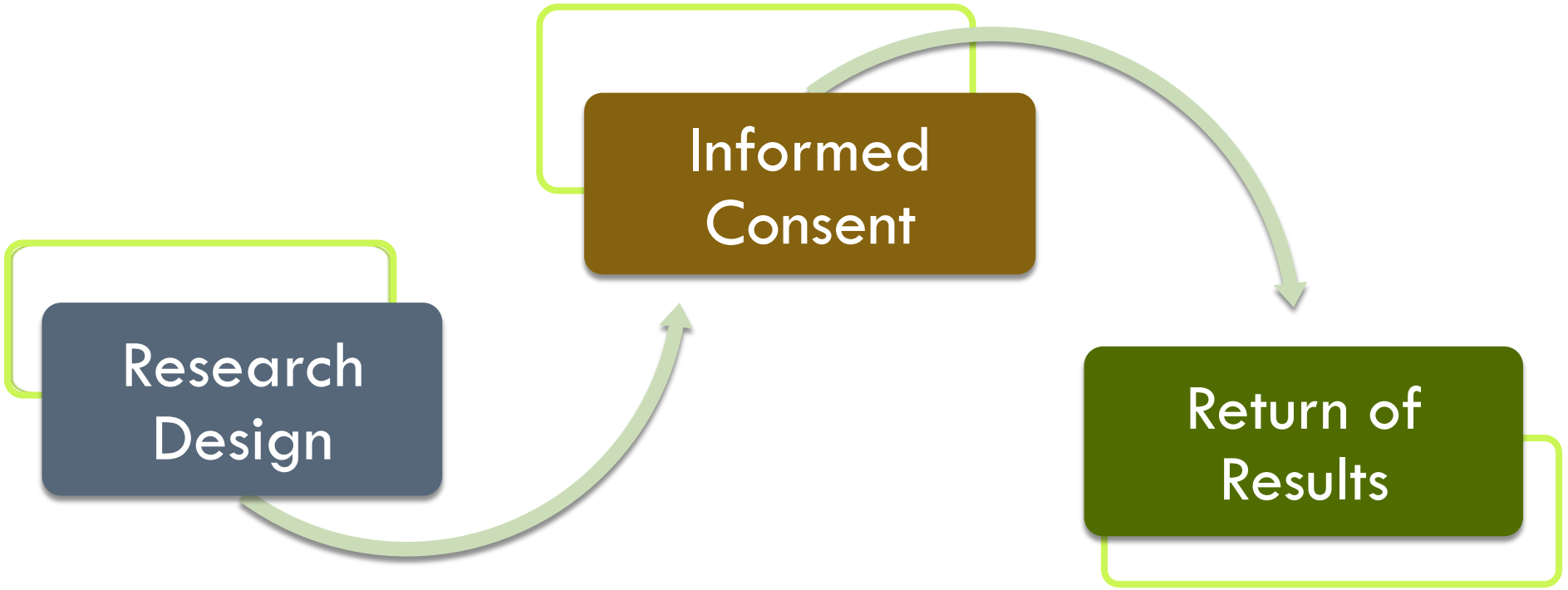
# Goal



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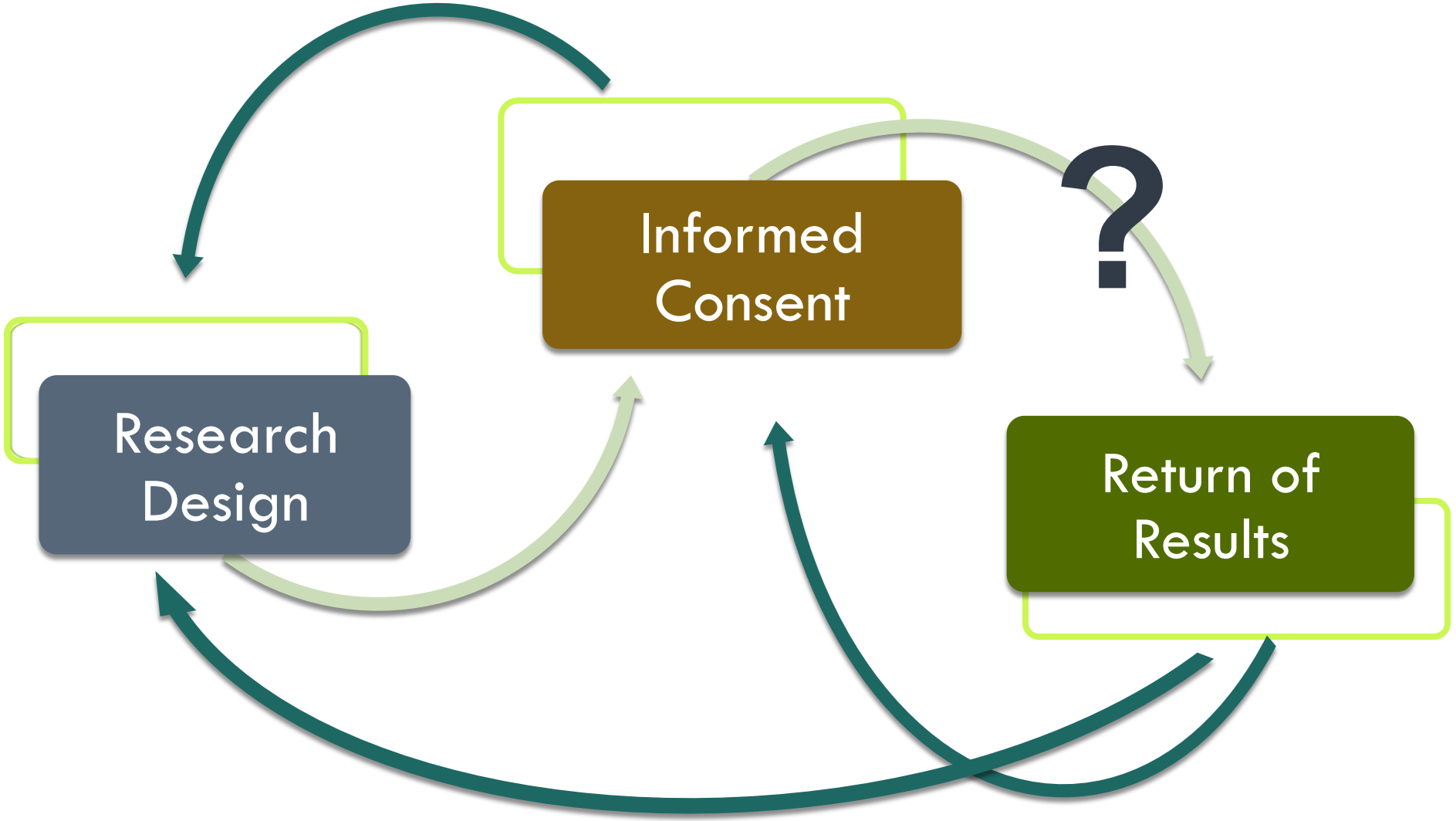

# Outline

- "What do I need to keep in mind as I approach (prospective) participants?"
- "How exactly do I go about getting participants' consent?"
- "What about…?
- "How do I return results to participants?"

# Outline

- Outline considerations in Whole-Exome Sequencing (**WES**) protocols
- Describe an approach to consent
- Discuss challenging populations and situations
- Explore options for returning results

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# Considering Informed Consent

- Informed consent as a process
- An opportunity for researcher-participant dialogue
  - Goals
  - Expectations
  - Plans
- Description of partnership
- Research goals drive informed consent process

# Data: inherent challenge

- Volume
  - Immense number of variants per participant
- Nature
  - Continuum from novel to well-characterized
  - Categorization from benign to deleterious
- Iterative generation
  - Downstream use and interrogation

# Data: inherent uncertainty

- Data generated are a moving target
- Fully conveying scale and scope is impossible
- Impact on participants varies tremendously
  - Impact on investigators may be non-trivial

# Outline

- General considerations in Whole-Exome Sequencing protocols (**WES**)
- Specific approach to consent
- Challenging populations and situations
- Returning results

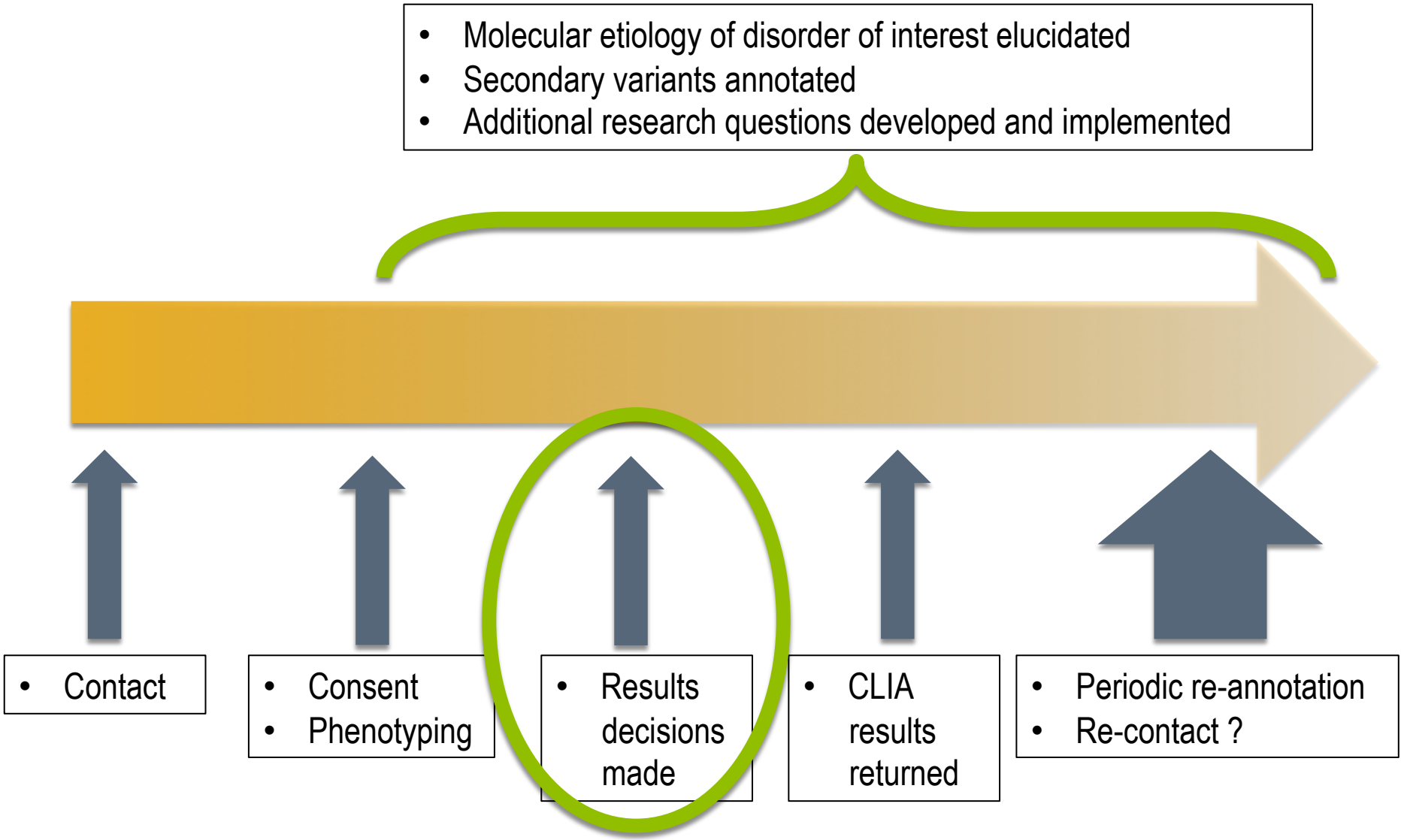
# Exome sequencing for gene discovery

- Protocol enrolls probands with rare disorders
- Broad eligibility criteria
- Trio approach **often** employed
  - But not always
- Comparisons made across probands
  - When possible
- Qualified results disclosure policy

# Consent Timeline

- Participant contact initiated
- Phone conversation describing study
- Consent form and one-page summary sent
- Follow-up phone call
- NIH visit
  - Phenotyping
  - Informed consent

# Protocol Timeline



# Results framed in terms of goal

- Broad categorization of results

| Primary Variant | Secondary Variants |
| --- | --- |
| Genetic cause of disorder under investigation | Everything else<br>Not goal of study<br>Inherent to methodology |

# Secondary Variants

- Further sub-categorized
  - Autosomal recessive disorders
  - Disease-causing mutations
    - Current/Future Onset
    - Treatment/Prevention
    - Surprising/Expected
  - Uncertain significance
  - Normal variation

# Secondary variants

- Ancillary to research goal
- Annotation is time-consuming
- Annotation is ongoing
- Represents departure from traditional paradigms
- Impact will vary across participants
- May not even be generated!

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**Defy complete *a priori* delineation and categorization**

# Choices about results

- Participants may elect to receive results (or not)
  - Primary variant
  - Secondary variants by category
- Each participant is independent actor
- Duty-to-warn exception explained

# Duty-to-warn

- Variants of this type are rare overall
- Not our intent to discover
- Research primacy explained

**Most participants identify with our intent**

# Familial implications

- Not all family members may undergo same interrogation
- Concerns regarding extended family
- Some approaches require communication among family members
- Minor children may undergo testing

# Alternatives and withdrawal

- Exome sequencing clinically available
- Will play role in clinical practice in future
- Withdrawal from protocol may not be simple

# Outline

- General considerations in Whole-Exome Sequencing protocols (**WES**)
- Specific approach to consent
- Challenging populations and situations
- Returning results

# Minor Probands

- One parent may consent on behalf
  - Specific consent form
- Some specific results may be returned
  - Carrier status
  - Actionable in childhood
  - Actionable in adulthood
    - Very specific conditions
- Asked to re-contact at age of majority

# Intellectual disability

- Legal guardian/surrogate decision-maker
- Proof required prior to consent
- May require ethics consult

# Intellectually impaired minors

- Thorough discussion at time of consent
- Current and future decision-making capacity discussed
- Any results may be returned per family's preference

# Not appropriate for some

- Research is not appropriate for everyone
  - Willing to engage over period of years
  - Stable/known family structure
  - Medical and social resources

# Outline

- General considerations in Whole-Exome Sequencing protocols (**WES**)
- Specific approach to consent
- Challenging populations and situations
- Returning results

# Results disclosure policies

- No results returned
- All results returned
- Some results returned
  - Limited or qualified disclosure

# Process

- Results possibilities reviewed, noted
- No commitment to preference at time of consent
- Annotation proceeds per study goal
- Participants re-contacted when available
- Categories reviewed and discussed
- Election made
- CLIA Validation
- Return to NIH for in-person review
  - May happen more than once

# Conclusions

- Most participants state preference to learn any results
  - Anecdotal evidence
- Participants align with researchers' goals
- Complexities are understandable
- Participant preferences vary by study design

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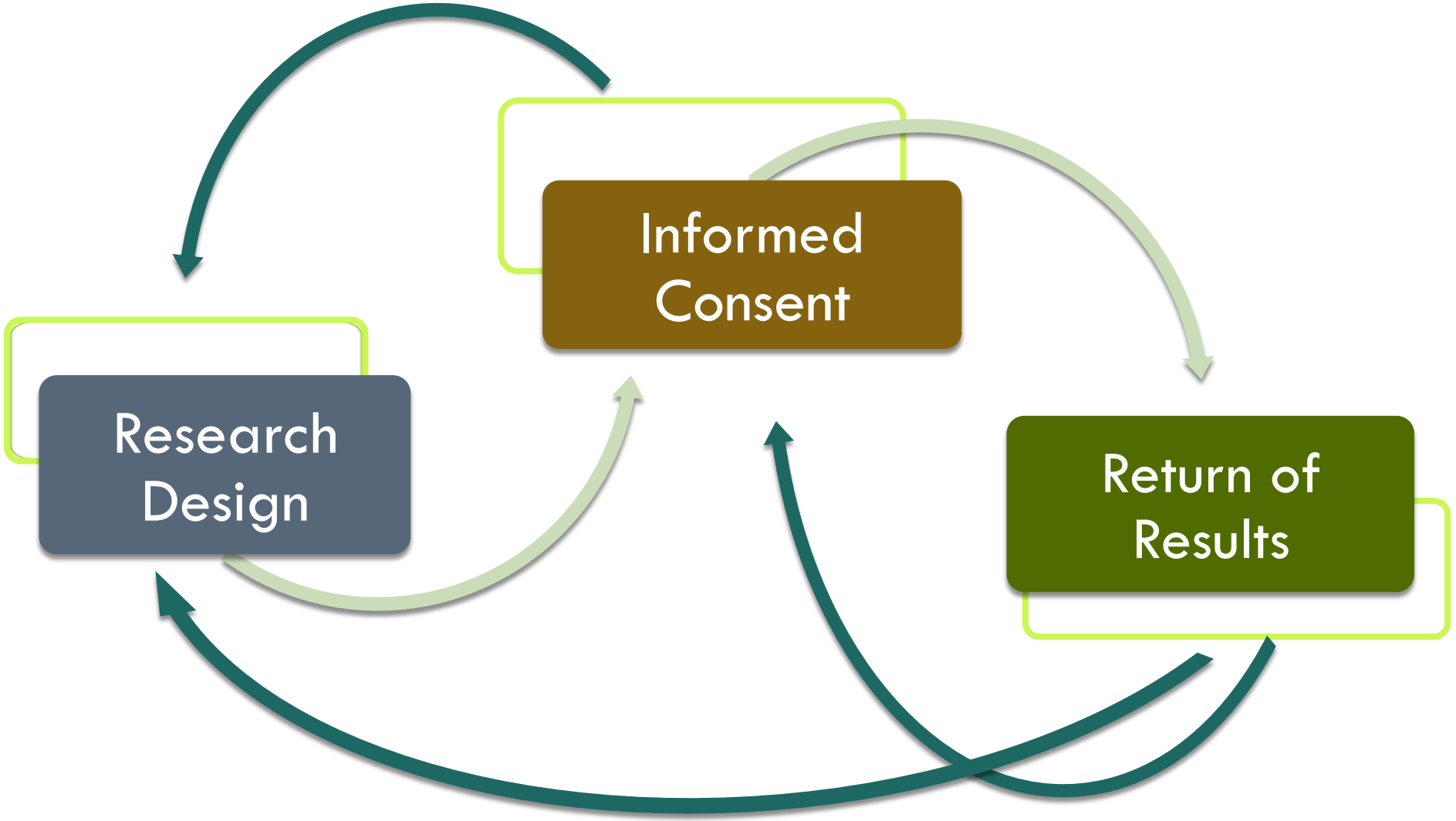

# Thank you!